

**What is claimed is:**

1. A compound of the structure or formula  $S-(L)_n-B$  wherein:
- a) S is an amino terminal signaling functional domain of PTH;
  - b) L is a linker molecule present n times; and
  - c) B is a C-terminal binding portion of PTH(1-34) or PTHrP(1-34).

2. The compound of claim 1, wherein said compound is an isolated polypeptide.

3. The isolated polypeptide of claim 2 wherein n is 1-9.

4. The isolated polypeptide of claim 2, wherein S is selected from the group consisting of PTH(1-9)(Ala Val Ser Glu Ile Gln Leu Met His (SEQ ID NO: 1), PTH(1-5)(Ala Val Ser Glu Ile (SEQ ID NO: 4) or PTH (1-11) (Ala Val Ser Glu Ile Gln Leu Met His Asn Leu (SEQ ID NO: 46).

5. The isolated polypeptide of claim 1, wherein L is selected from the group consisting of Gly<sub>5</sub>, Gly<sub>7</sub> and Gly<sub>9</sub>.

6. The isolated polypeptide of claim 1, wherein B is selected from the group consisting of PTH(15-31)(Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:2), PTH(17-31)(Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:4), PTHrP(15-31)(Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:8), and PTHrP(17-31)(Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:12).

7. The isolated polypeptide of claim 1 selected from the group consisting of PG5: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Leu Asn Ser Met

Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:3), PG9: Ala Val Ser Glu Ile Gly Gly Gly Gly Gly Gly Gly Gly (Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:5), PG7: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Gly Gly Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:6), PrPG5: Ala Val Ser Glu His Gln Leu Leu His Gly Gly Gly Gly Gly (Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:9), PrPG9: Ala Val Ser Glu His Gly Gly Gly Gly Gly Gly Gly Gly Gly (Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:11) and PrPG7: Ala Val Ser Glu His Gln Leu Leu His Gly Gly Gly Gly Gly Gly Gly Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:13) and functional derivatives thereof.

8. The isolated polypeptide of claim 2, wherein said polypeptide is selected from the group consisting of PG5 (PTH (1-9)-(Gly)<sub>5</sub>-PTH(15-31) (SEQ ID NO:9), PG7 (PTH (1-9)-(Gly)<sub>7</sub>-PTH(17-31) (SEQ ID NO:11), PG9 (PTH (1-5)-(Gly)<sub>9</sub>-PTH(15-31) (SEQ ID NO:13). and functional derivatives thereof.

9. The isolated polypeptide of claim 8 wherein there is a single amino acid substitution.

10. The isolated polypeptide of claim 2, wherein:

- (a) S is X Val X Glu X X X X His (SEQ ID NO: 42), wherein X is an amino acid;
- (b) L is 5-10 glycine residues; and
- (c) B is X X X X X Arg X X Trp X Leu X Lys Leu X X Val (SEQ ID NO: 43), wherein X is an amino acid.

11. The isolated polypeptide of claim 2, wherein:

- (d) S is Ser Val Ser Glu Ile Gln Leu Met His (SEQ ID NO: 44);

(e) L is 5-10 glycine residues; and

(f) B is as Leu Asn Ser-Met Glu Arg Val Glu Trp Leu Arg Lys Lys  
Leu Gln Asp Val (SEQ ID NO: 45).

5 12. The isolated polypeptide of claim 1, selected from the group consisting  
of: PG5 (PTH (1-9)-(Gly)<sub>5</sub>-PTH(15-31) (SEQ ID NO:9), PG7 (PTH (1-9)-  
(Gly)<sub>7</sub>-PTH(17-31) (SEQ ID NO:11) and PG9 (PTH (1-5)-(Gly)<sub>9</sub>-P TH(15-31)  
(SEQ ID NO:13).

13. The isolated polypeptide of claim 2, wherein said polypeptide is a  
biologically active polypeptide.

10 14. The isolated polypeptide of claim 2, encoded by a nucleic acid sequence  
selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:15 and  
nucleic acid (SEQ ID NO:16) sequence.

15. An isolated nucleic acid sequence encoding the polypeptide of any one  
of claims 2-13.

15 16. An isolated polypeptide of the structure of formula  $R_1-S-(L)_n-R$ , or  
 $S-(L)_n-R$  wherein:

- 20
- a)  $R_1$  is the PTH-1 receptor signal sequence;
  - b) S is an amino-terminal ligand signaling peptide;
  - c) L is a linker molecule present n times, where n is a positive integer  
1-10, most preferably 4; and
  - d) R is PTH-1 receptor sequence or a portion of the receptor  
sequence.

17. The isolated polypeptide of claim 16, wherein  $R_1$  is the PTH-1 receptor(1-25) peptide, S is the PTH(1-9) peptide, L is Gly, wherein N is 4; and R is the PTH-1 receptor (182-end).

18. The isolated polypeptide of claim 16 having the the formula  $S-(L)_n-R$ , wherein the  $R_1$  moiety has been cleaved.

19. An isolated nucleic acid sequence encoding the polypeptide of claim 16.

20. An isolated polypeptide of the formula S-R, wherein:

1. S is an amino-terminal signaling polypeptide; and
2. R is a carboxy-terminal receptor polypeptide.

21. The isolated polypeptide of Claim 20, wherein S is the amino-terminal signaling polypeptide X Val X Glu X X X X His, wherein X is an amino acid.

22. An isolated polypeptide comprising a sequence selected from the group the of sequences consisting of SEQ ID NO: 37, SEQ ID NO:39 and SEQ ID NO: 41.

23. An isolated nucleic acid sequence encoding a polypeptide sequence of claim 22.

24. An isolated nucleic acid sequence selected from the group consisting of SEQ ID NO:36, SEQ ID NO:38 and SEQ ID NO:40.

25. An isolated nucleic acid sequence, wherein said sequence is at least 95% identical to or binds under stringent conditions to a sequence of claim 24.

26. A recombinant vector comprising a nucleic acid sequence of claim 15

27. A recombinant host cell comprising the DNA of claim 26.

28. A recombinant vector comprising a nucleic acid sequence of claim 23.

29. A recombinant host cell comprising the DNA of claim 28.

30 A method for treating mammalian conditions characterized by decreases  
5 in bone mass, wherein said method comprises administering to a subject in need  
thereof an effective bone mass-increasing amount of the polypeptide of any one  
of claims 2, 16 or 20.

31. A method for determining rates of bone reformation, bone resorption  
and/or bone remodeling comprising administering to a patient an effective amount  
10 of a polypeptide of any one of claims 2, 20 or 40 and determining the uptake of  
said peptide into the bone of said patient.

32. The method of claim 30, wherein said effective bone mass-increasing  
amount of said peptide is administered by providing to the patient DNA encoding  
said peptide and expressing said peptide *in vivo*.

33. The method of claim 32, wherein the condition to be treated is  
osteoporosis.

34. The method of claim 24, wherein the effective amount of said polypeptide  
for increasing bone mass is from about 0.01 µg/kg/day to about 1.0 µg/kg/day.

35. A method of treating diseases and disorders associated with decreased  
Tether1 activity comprising administering an effective amount of the polypeptide  
20 of any one of claims 2, 20 or 40, or an agonist thereof to a patient in need thereof

36. A method of increasing cAMP in a mammalian cell having PTH-1 receptors, comprising contacting said cell with a sufficient amount of the polypeptide of any one of claims 2, 20 or 40 to increase cAMP.

37. The isolated polypeptide of claim 2 wherein B is 10-20 amino acids in length.

38. A method for screening for a peptide or non-peptide PTH agonist comprising:

- a) binding a polypeptide of claim 16 to a potential agonist; and
- b) isolating said potential agonist from said polypeptide.

39. The method of claim 38, wherein said polypeptide is Tether 1 or rδNt.

40. An isolated polypeptide, wherein said polypeptide is obtained by the method of claim 38.